REMARKS

The following remarks are based on discussions with Examiners Afremova and Lankford during the September 1, 2004 interview. The remarks are organized under appropriate subheadings for the convenience of the Examiner.

References Cited in the Office Action Made Final

During the interview, Applicants discussed with the Examiners references cited by Examiner Afremova in the Office Action Made Final. In particular, Applicants discussed U.S. Patent Application No. 2002/0168765 A1 by Prockop, D.J., *et al.* (hereinafter "Prockop"), WO 01/34167 by Prockop, D.J., *et al.* (hereinafter "Prockop II"), WO 01/11011 by Furcht, L.T., *et al.* (hereinafter "Furcht") and Colter, D.C., *et al.*, *Proc. Natl. Acad. Sci USA*, 97:3213-3218 (2000) (hereinafter "Colter"). The Examiners stated that Applicant's claimed cell population is obvious to one of skill in the art in view of the previously cited references, in particular, Prockop, Prockop II, Colter and Furcht. In support of the rejection, the Examiners specifically referenced Table 1 and Figures 2, 4, 5, 6 and 7 of Colter, which correspond to Table 2 and Figures 18, 20, 21, 22 and 23, respectively, of Prockop II. The Examiners further stated that Furcht taught selection techniques using antibodies and cell sorting that would be used by one skilled in the art to select a cell population wherein greater than about 91% of the cells in the cell population co-express CD49c and CD90, and wherein the cell population has a doubling rate less than about 30 hours.

Applicants' claimed invention, as set forth in pending Claims 14, 19-21, 23, 25 and 26, is directed to an isolated cell population derived from bone marrow, wherein greater than about 91% of the cells in the cell population co-express CD49c and CD90, and wherein the cell population has a doubling rate less than about 30 hours.

During the interview, Applicants distinguished their invention, as set forth in pending Claims 14, 19, 20, 21, 23, 25 and 26, from the disclosure of Prockop, Prockop II and Colter, which describe cell cultures of bone marrow stromal cells (MSC cells) that contain rapidly cell-renewing stem cells (RS cells) and large, more mature cells (mMSC cells). The RS cells of Prockop, Prockop II and Colter are further subdivided into RS-1 and RS-2 cells that differ in the

presence of CD90. As shown in Table 1 of Colter and Table 2 of Prockop II, RS-1 cells are "dim," RS-2 cells are "negative" and mMSCs cells are "positive" for CD90. Prockop, Prockop II and Colter disclose a population of cells that changes in the percent of RS-1, RS-2 and mMSC cells and, thus, the percent of CD90 positive cells and doubling rates, over about a 14 day culture period, as depicted in Figure 4 of Colter and Figure 20 of Prockop II.

As shown in Figure 4 of Colter and in Figure 20 of Prockop II, at about days 5, 7 and 10 of culture, the cell population is composed of RS-1 cells ("dim" for CD90), RS-2 ("negative" for CD 90) and mMSC cells ("positive" for CD 90) and at about day 14 of culture, the cell population is largely composed on RS-1 cells ("dim" for CD90) and mMSC cells ("positive" for CD90).

As requested by the Examiners during the interview, Applicants determined the doubling rate for the population of cells depicted in Figure 4 of Colter and Figure 20 of Prockop II after about days 5, 7, 10 and 14 in culture. Estimates of the number of RS-1, RS-2 and mMSC cells were made based on extrapolation from the data points on days 5, 7, 10 and 14 to the y-axis (cell number). No estimate could be made of the number of RS-1, RS-2 and mMSC cells at day 0 of culture because the data points were aggregated and not discernable.

The total number of cells on days 5, 7, 10 and 14 was obtained by totaling the number of RS-1, RS-2 and mMSC cells. The total number of CD90 positive cells on days 5, 7, 10 and 14 was obtained by adding the number of RS-1 ("dim" for CD90) and mMSC ("positive" for CD90) cells together. The percentage of CD90 positive cells at days 5, 7, 10 and 14 was obtained by dividing the number of CD90 positive cells by the total number of cells.

Table 1, below, is a summary of the results of these calculations:

TABLE 1

Cell type		Number of cells Day 5	Day 7	Day 10	Day 14
RS1	(CD90 dim)	63.0	188.0	344.0	2588.0
RS2	(CD90 negative)	500.0	1625.0	1125.0	118.0
mMSC	(CD90 positive)	375.0	1125.0	3750.0	15294.0
Total CD90 positive (RS1/mMSC)		438.0	1313.0	4094.0	17882.0
Total Cells (RS1/RS2/mMSC)		938.0	2938.0	5219.0	18000.0
Percent CD90 positive cells		46.7	44.7	78.4	99.3

Table 2, below, represents the doubling rate, in hours, for the entire population of cells.

TABLE 2

Doubling rate of mixed population of cells*

	Number of cells from day 5-7	from day 7-10	from day 10-14
Time (hr)	48.0	72.0	96.0
Starting cell number	938.0	2938.0	5219.0
Ending cell number	2938.0	5219.0	18000.0
Number population doublings	1.6	0.8	1.8
Doubling rate (hr)	29.1	86.9	53.7

* RS-1, RS-2 and mMSC cells

The number of population doublings on days 5, 7, 10 and 14, as shown in Table 2, was determined by calculating how many times the cells duplicated based on the number of cells at the beginning of a particular time period to the number of cells at the end of that period. For example, the number of population doublings for a cell population from day 5 to day 7 in culture was determined from a starting cell number at day 5 to the ending cell number at day 7 (2 days, or 48 hours, in culture). Likewise, the number of population doublings for a cell population from day 7 to day 10 in culture was determined from a starting cell number at day 7 to the ending cell number at day 10 (3 days, or 72 hours, in culture). Similarly, the number of population doublings for a cell population from day 10 to day 14 in culture was determined from a starting

cell number at day 10 to the ending cell number at day 14 (4 days, or 96 hours, in culture). By way of illustration, as shown in Table 2, *supra*, from day 10-14, the starting number of cells was about 5200, that doubles to about 10,400, that, in turn, doubles to about 20,800 so that the ending cell number represents a population doubling of about 1.8. The doubling rate for the cell populations was determined by multiplying the total number of days in culture by 24 and dividing the result by the number of doublings.

As shown in Table 2, the doubling rate for a mixed population of RS-1 ("dim" for CD90), RS-2 ("negative" for CD90) and mMSC ("positive" for CD90) cells from day 5 to day 7 was about 30 hours when the percent of CD90 positive cells varied from about 47% at day 5 of culture to about 45% at day 7 of culture (see Table 1). Thus, the cell population, starting from day 5, described by Prockop, Prockop II and Colter that has a doubling rate of about 30 hours is not a cell population wherein greater than about 91% of the cells in the cell population co-express CD49c and CD90, which is the subject matter of Applicants' claimed invention. Similarly, the doubling rate for a mixed population of RS-1 ("dim" for CD90), RS-2 ("negative" for CD90) and mMSC ("positive" for CD90) cells from day 7 to day 10 was about 87 hours when the percent of CD90 positive cells varied from about 45% at day 7 of culture to about 78% at day 10 of culture (see Table 1). Therefore, this cell population, starting from day 7, described by Prockop, Prockop II and Colter also is not an isolated cell population wherein greater than about 91% of the cells in the cell population co-express CD49c and CD90, and wherein the cell population has a doubling rate less than about 30 hours, which is the subject matter of Applicants' claimed invention. Likewise, the doubling rate for a mixed population of RS-1 ("dim" CD90), RS-2 ("negative" CD90) and mMSC ("positive" CD 90) cells from day 10 to day 14 was about 54 hours when the percent of CD90 positive cells varied from about 78% at day 10 of culture to about 99% at day 14 of culture (see Table 1). Therefore, as with the earlier populations, this cell population, starting from day 10, described by Prockop, Prockop II and Colter, is not an isolated an isolated cell population wherein greater than about 91% of the cells in the cell population co-express CD49c and CD90, and wherein the cell population has a doubling rate less than about 30 hours, which is the subject matter of Applicants' claimed invention.

There is no suggestion in Prockop, Prockop II or Colter, individually or in any combination, of a cell population wherein all of the cells co-express CD90 and CD49c. The cells of Prockop, Prockop II and Colter are a mixed population of cells, in which cells vary in CD90 expression and doubling rate. Prockop, Prockop II or Colter do not describe a population of cells in which each cell expresses CD49c and CD90. Further, in view of the fact that population doubling time slows as the percentage of CD90 "dim" or "positive" cells increases, extrapolation of the data of Prockop, Prockop II and Colter beyond 14 days does not disclose or suggest a population of cells having greater than 91% of the cells, with a doubling rate of about 30 hours, as shown in Tables 1 and 2, *supra*.

During the interview, it was suggested by the Examiners that CD90 "dim" and/or "positive" cells could be selected from the mixed populations taught to thereby culture a population of cells consisting essentially of such cells and having a doubling time of less than or equal to 30 hours. In reply to this position, Applicants have selected, from the data of Tables 1 and 2, the population doubling rates of only CD90 "dim" and "positive" cells. The selected data is presented below in Table 3. As can be seen in Table 3, even if this data is taken out of the context of the mixed population in which the cells of Table 3 were cultured, there still is no instance in which the cell population had a doubling time of less than 30 hours. For example, Table 3 represents the doubling rate, in hours, for cell populations that were "dim" (RS-1 cells) or "positive" (mMSC cells) for CD90.

TABLE 3

Doubling rate for CD90 positive cells*

	Number of cells		
	from day 5-7	from day 7-10	from day 10-14
Time (hr)	48.0	72.0	96.0
Starting cell number	438.0	1313.0	4094.0
Ending cell number	1313.0	4094.0	17882.0
Number population doublings	1.6	1.6	2.1
Doubling rate (hr)	30.3	43.9	45.1

*RS-1 and mMSC cells

As shown in Table 3, the doubling rate for CD90 positive cells (RS-1 and mMSC cells) from day 5 to day 7 of culture was about 30 hours, however, as shown in Table 1, the percent of CD90 cells at this time in culture and with this doubling rate varied from about 47% on day 5 and about 45% on day 7. As shown in Table 3, the doubling rate for CD90 cells (RS-1 and mMSC) from day 7 to day 10 of culture was about 44 hours, when the percent of CD90 cells varied from about 45% on day 7 and about 78% on day 10 (see Table 1). As shown in Table 3, the doubling rate for CD90 cells (RS-1 and mMSC) from day 10 to day 14 of culture was about 45 hours, however, as shown in Table 1, the percent of CD90 cells at this time in culture and with this doubling rate varied from about 79% on day 10 and about 99% on day 14. In addition, as described in Prockop, Prockop II and Colter, a cell population selected from the day 14 population repeatedly grew to have a mixed population, as reflected in Figure 4 of Colter.

Unlike the cell populations of Prockop, Prockop II and Colter, Applicants' claimed cell population is a stable cell population that does not vary in doubling rate or the number of CD49c and CD90 cells with time in culture. Applicants' cell population is consistently a cell population wherein greater than about 91% of the cells in the cell population co-express CD49c and CD90, and wherein the cell population has a doubling rate less than about 30 hours

Further, none of the references cited by the Examiner teach an isolated cell population derived from bone marrow that co-express CD49c and CD90.

Therefore, neither Prockop I, Prockop II and Colter, alone or in any combination, disclose, expressly or inherently, or suggest a cell population isolated from bone marrow wherein greater than about 91% of the cells of the cell populations co-express CD49c and CD90 and wherein the cell population has a doubling rate of less than about 30 hours, which is the subject matter of Applicants' claimed invention.

Furcht describes multipotent adult stem cells (MASC cells) including MASC cells derived from bone marrow aspirates. On page 24, lines 20-22, and as shown in Figure 2, Furcht describes a population of cells derived from bone marrow which have a doubling time of 36-48 hours for the initial 20-30 cell doublings followed by cell doubling time of 60-72 hours. On page 73, lines 10-18, Furcht describes a population of cells with a doubling time of 48-60 hours which stain positive with antibodies against several cell markers including CDw90.

Furcht does not remedy the deficiencies of Prockop, Prockop II or Colter. Specifically, there is no disclosure or suggestion in Prockop, Prockop II or Furcht, taken either separately or in any combination, of an isolated cell population derived from bone marrow, wherein greater than about 91% of the cells of the cell population co-express CD49c and CD90 and wherein the cell population has a doubling rate of less than about 30 hours. Thus, neither Prockop, Prockop II, Colter or Furcht, taken either separately or in any combination, disclose or suggest Applicants' claimed invention.

Therefore, the Examiner has not established a *prima facie* case of obviousness since there is no suggestion or teaching, inherently or expressly, in Prockop, Prockop II, Colter or Furcht and U.S. Patent No. 5,837,539, issued to Caplan, A.I., *et al.* (hereinafter "Caplan"), van den Bos, C., *et al.*, *Cell Tissue Res.*, 293:463-470 (1998) (hereinafter "Bos") and Gartel, A.L., *et al.*, *Exp. Cell Res.*, 246:280-289 (1999) (hereinafter "Gartel"), the other references cited by the Examiner in the Office Action made Final, separately or in any combination, of Applicants' claimed cell population, as set forth in pending Claims 14, 19-21, 23, 25 and 26.

Applicants' claimed invention, as set forth in Claims 14, 19-21, 23, 25 and 26, meets requirements of 35 U.S.C. § 103(a).

Reference Previously Cited by the Examiner in an Office Action

Examiner Afremova asked Applicants to comment on Ross, J.A., *et al.*, *Advances in Peritoneal Dialysis 14*:25-30 (1998) (hereinafter "Ross"), previously cited in an Office Action mailed from the USPTO on July 24, 2003 in support of under 35 U.S.C. § 102(b), which Examiner Afremova withdrew in the Office Action Made Final. In particular, the Examiner stated that Applicants' claimed cell population could be interpreted to be a product-by-process claim and, despite the fact that Ross does not disclose a cell population derived from bone marrow, the Ross did disclose a human mesothelial cell population that co-expresses CD49c and CD90.

Ross describes a primary cell culture of human peritoneal mesothelial cells, obtained from biopsies of human omentum, which express, to varying percentages, CD49c and CD90. Ross states on page 25, that human mesothelial cells are "capable" of producing IL-6 in response to an appropriate stimulus.

Applicants discussed with the Examiners at the interview that there is no express or inherent teaching in Ross of an isolated cell population derived from bone marrow, wherein greater than about 91% of the cells of the isolated cell population co-express CD49c and CD90 and wherein the isolated cell population has a doubling rate of less than about 30 hours. Therefore, Ross does not disclose the subject matter of Applicants' claimed invention.

In addition, Applicants noted that pending Claims 14, 19, 20, 21, 23, 25 and 26, are not product by process claims since there is no method step in the claim.

SUMMARIES AND CONCLUSIONS

The subject matter of Claims 14, 19-21, 23, 25 and 26 meets the requirements of 35 U.S.C. § 103(a) in view of Prockop, Prockop II, Colter and Furcht, which were discussed with Examiners Afremova and Lankford. In addition, as discussed in the Reply filed July 26, 2004, the subject matter of Claims 14, 19-21, 23, 25 and 26 meets the requirements of 35 U.S.C. § 103(a) in view of Prockop, Prockop II, Colter and Furcht in light of evidence by Caplan and Colter and in further view of Bos and Gartel. Therefore, Applicants respectfully request reconsideration and allowance of the claims under consideration.

If the Examiner feels a telephone conference would expedite prosecution of this application, she is invited to call Applicants' undersigned attorney.

Respectfully submitted,

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